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  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

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L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN

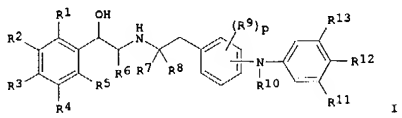
ACCESSION NUMBER: 140:16568 CA
TITLE: Preparation of aryl aniline .beta.-2 adrenergic receptor agonists
INVENTOR(S): Moran, Edmund J.; Jacobsen, John R.; Leadbetter, Michael R.; Nodwell, Matthew B.; Trapp, Sean G.; Aggen, James; Church, Timothy J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 68 pp., Cont.-in-part of U.S. Ser. No. 292,835.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003229058 | A1 | 20031211 | US 2003-431762 | 20030508 |
| US 6670376 | B1 | 20031230 | US 2002-292835 | 20021112 |
| US 2004059116 | A1 | 20040325 | US 2003-642926 | 20030818 |
| US 2004063755 | A1 | 20040401 | US 2003-643196 | 20030818 |

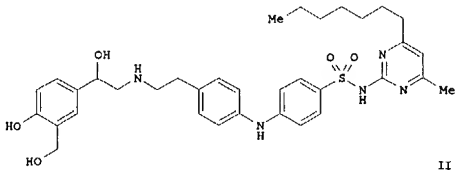
PRIORITY APPLN. INFO.: US 2001-338194P P 20011113
US 2001-343771P P 20011228
US 2002-292835 A2 20021112
US 2002-292211 A1 20021112

OTHER SOURCE(S): MARPAT 140:16568
GI

L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)



I



II

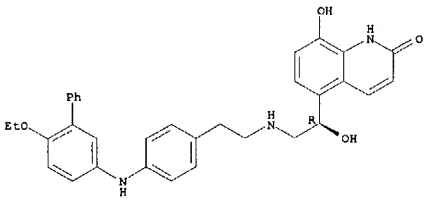
AB Title compds. I [R1-5 = H, alk(en/yn)yl, cycloalkyl, heterocyclyl, etc.; R6 = H, alkyl, alkoxy; R7 = H, alkyl; R8 = H, alkyl; R9 = alk(en/yn)yl, (hetero)aryl, etc.; R10 = H, alkyl; R11-13 = H, (cyclo)alkyl, alkenyl, alkynyl, (hetero)aryl, etc.; p = 0-4] are prepd. For instance, the di-Me ketal of 4-hydroxy-3-hydroxymethyl-.alpha.-bromoacetophenone (prepn. given) is reacted with 4-bromophenethylamine (CH2Cl2, Et3N) followed by 4,4'-dimethoxychlorodiphenylamine and subsequently reduced (THF, NaBH4). The resulting protected amino alc. is then coupled with N-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide (PhMe, dppf, Pd2dba3, 80.degree., 5 h) and then deprotected with HOAc (80.degree., 5 h) to give II. All of the compds. tested demonstrated greater binding at the .beta.2 adrenergic receptor than at the .beta.1 adrenergic receptor, i.e., Ki(.beta.1) > Ki(.beta.2); many with a selectivity greater than 20. I are useful for the treatment of pulmonary diseases.

IT **530084-66-3P 530084-87-8P 530117-33-0P 530117-43-2P 530118-10-6P 530118-11-7P 530118-12-8P 530118-13-9P 530118-17-3P 530118-19-5P 530118-20-8P 530118-21-9P 530118-24-2P 530118-25-3P 631914-89-1P 631915-04-3P 631915-05-4P 631915-06-5P 631915-07-6P 631915-08-7P 631915-09-8P 631915-10-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)
(prepn. of aryl aniline .beta.-2 adrenergic receptor agonists for treatment of pulmonary disorders)

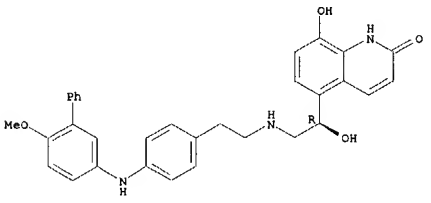
RN 530084-66-3 CA
CN 2(1H)-Quinolinone, 5-[(1R)-2-[[2-[4-[(6-ethoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]-1-hydroxyethyl]-8-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 530084-87-8 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[(6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]ethyl]- (9CI) (CA INDEX NAME)

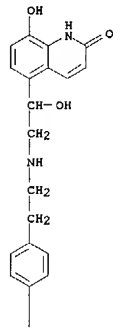
Absolute stereochemistry.



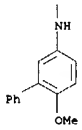
RN 530117-33-0 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[1-hydroxy-2-[[2-[4-[(6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]ethyl]-, hydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

PAGE 1-A



PAGE 2-A

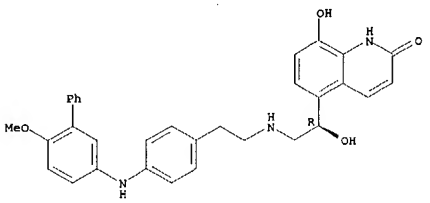


●x HCl

RN 530117-43-2 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[(6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]ethyl]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

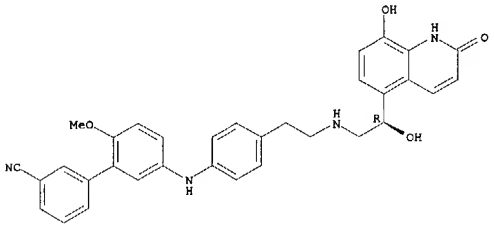
L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)



●x HCl

RN 530118-10-6 CA
CN [1,1'-Biphenyl]-3-carbonitrile, 5'-[[4-[2-[[(2R)-2-(1,2-dihydro-8-hydroxy-2-oxo-5-quinolinyl)-2-hydroxyethyl]amino]ethyl]phenyl]amino]-2'-methoxy- (9CI) (CA INDEX NAME)

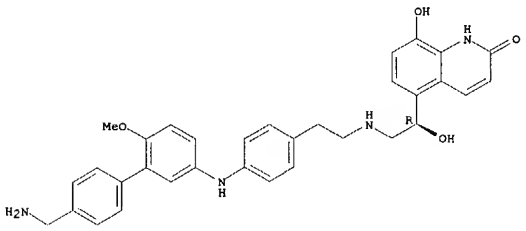
Absolute stereochemistry.



RN 530118-11-7 CA
CN [1,1'-Biphenyl]-3-carbonitrile, 5'-[[4-[2-[[(2R)-2-(1,2-dihydro-8-hydroxy-2-oxo-5-quinolinyl)-2-hydroxyethyl]amino]ethyl]phenyl]amino]-2'-methoxy-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

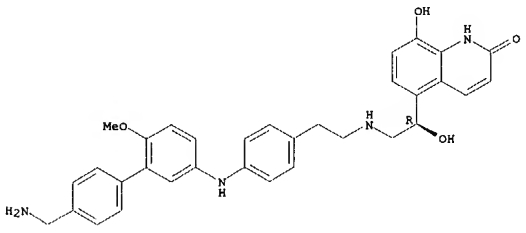


RN 530118-13-9 CA
CN 2(1H)-Quinolinone, 5-[(1R)-2-[[2-[4-[[4'-(aminomethyl)-6-methoxy[1,1'-biphenyl]-3-yl]amino]phenyl]ethyl]amino]-1-hydroxyethyl]-8-hydroxy-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 530118-12-8
CMF C33 H34 N4 O4

Absolute stereochemistry.



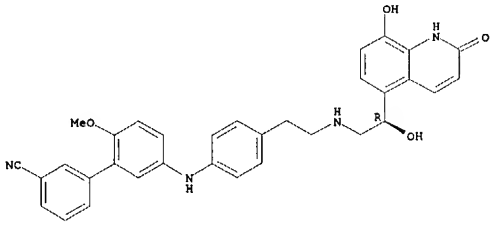
CM 2

CRN 76-05-1
CMF C2 H F3 O2



L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)
CRN 530118-10-6
CMF C33 H30 N4 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
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RN 530118-12-8 CA
CN 2(1H)-Quinolinone, 5-[(1R)-2-[[2-[4-[[4'-(aminomethyl)-6-methoxy[1,1'-biphenyl]-3-yl]amino]phenyl]ethyl]amino]-1-hydroxyethyl]-8-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

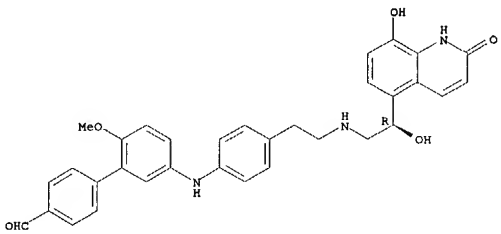
L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

RN 530118-17-3 CA
CN [1,1'-Biphenyl]-4-carboxaldehyde, 5'-[[4-[2-[[(2R)-2-(1,2-dihydro-8-hydroxy-2-oxo-5-quinolinyl)-2-hydroxyethyl]amino]ethyl]phenyl]amino]-2'-methoxy-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 530118-16-2
CMF C33 H31 N3 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

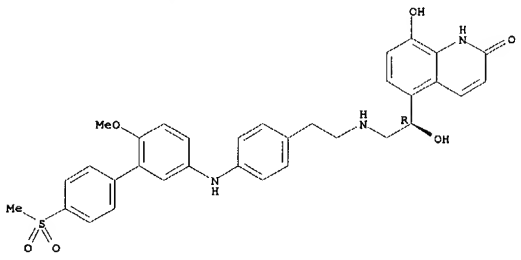
RN 530118-19-5 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[[6-methoxy-4'-(methylsulfonyl)[1,1'-biphenyl]-3-yl]amino]phenyl]ethyl]amino]ethyl]-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 530118-18-4

L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)
CMF C33 H33 N3 O6 S

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

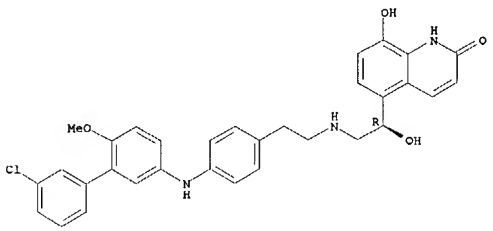
RN 530118-20-8 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[(4'-hydroxy-6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

RN 530118-24-2 CA
CN 2(1H)-Quinolinone,
5-[(1R)-2-[[2-[4-[(3'-chloro-6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]-1-hydroxyethyl]-8-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



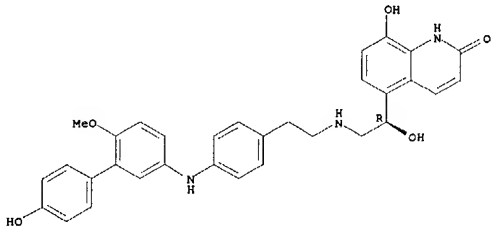
RN 530118-25-3 CA
CN 2(1H)-Quinolinone,
5-[(1R)-2-[[2-[4-[(3'-chloro-6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]-1-hydroxyethyl]-8-hydroxy-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 530118-24-2
CMF C32 H30 Cl N3 O4

Absolute stereochemistry.

L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

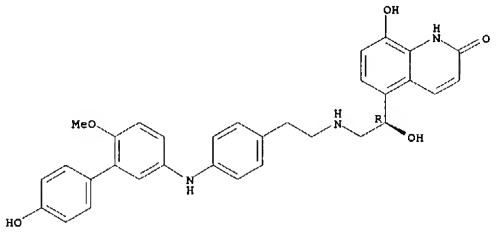


RN 530118-21-9 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[(4'-hydroxy-6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 530118-20-8
CMF C32 H31 N3 O5

Absolute stereochemistry.



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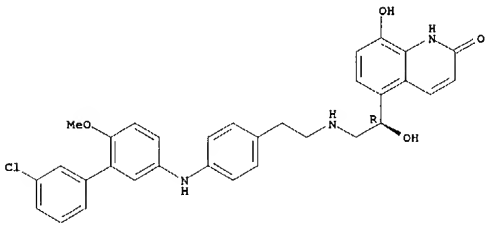
CRN 76-05-1
CMF C2 H F3 O2

L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)



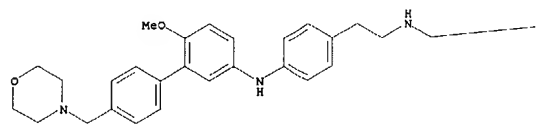
CM 2

CRN 76-05-1
CMF C2 H F3 O2

RN 631914-89-1 CA
CN 2(1H)-Quinolinone,
8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[(6-methoxy-4'-(4-morpholinylmethyl)[1,1'-biphenyl]-3-yl]amino]phenyl]ethyl]amino]ethyl]- (9CI) (CA INDEX NAME)

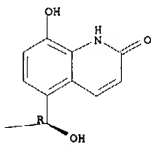
Absolute stereochemistry.

PAGE 1-A



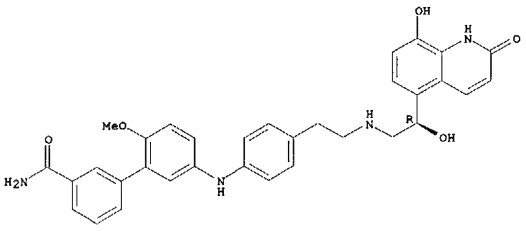
L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

PAGE 1-B



RN 631915-04-3 CA
CN [1,1'-Biphenyl]-3-carboxamide,
5'-[[4-[2-[[(2R)-2-(1,2-dihydro-8-hydroxy-2-oxo-5-quinolinyl)-2-hydroxyethyl]amino]ethyl]phenyl]amino]-2'-methoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 631915-05-4 CA
CN 2(1H)-Quinolinone, 5-[(1R)-2-[[2-[4-[[3'-(aminomethyl)-6-methoxy[1,1'-biphenyl]-3-yl]amino]phenyl]ethyl]amino]-1-hydroxyethyl]-8-hydroxy-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

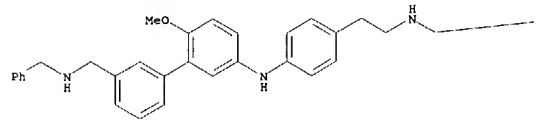
PAGE 1-B



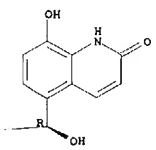
RN 631915-07-6 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[[6-methoxy-3'-[[(phenylmethyl)amino]methyl][1,1'-biphenyl]-3-yl]amino]phenyl]ethyl]amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



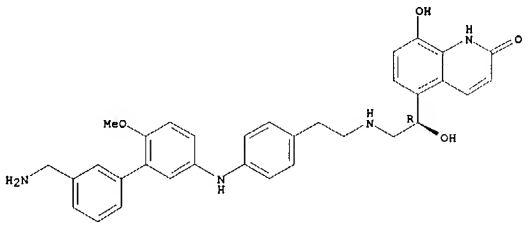
PAGE 1-B



RN 631915-08-7 CA
CN 2(1H)-Quinolinone, 5-[(1R)-2-[[2-[4-[[3'-[(dimethylamino)methyl]-6-methoxy[1,1'-biphenyl]-3-yl]amino]phenyl]ethyl]amino]-1-hydroxyethyl]-8-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

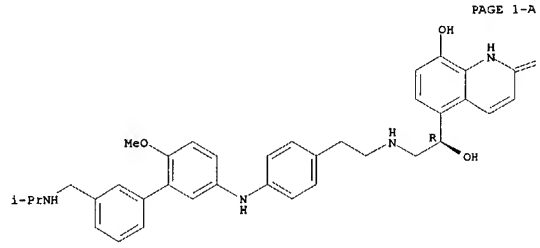


●x HCl

RN 631915-06-5 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[[6-methoxy-3'-[[(1-methylethyl)amino]methyl][1,1'-biphenyl]-3-yl]amino]phenyl]ethyl]amino]ethyl]- (9CI) (CA INDEX NAME)

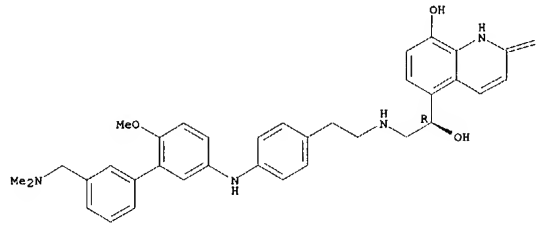
Absolute stereochemistry.

PAGE 1-A



L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

PAGE 1-A



PAGE 1-B

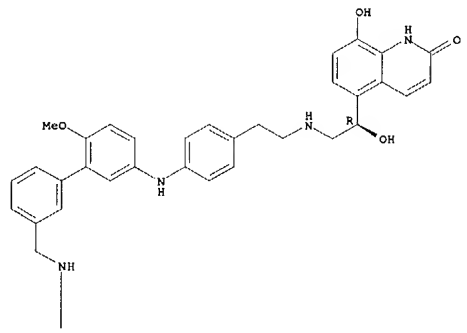


RN 631915-09-8 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[[6-methoxy-3'-[[(3-pyridinylmethyl)amino]methyl][1,1'-biphenyl]-3-yl]amino]phenyl]ethyl]amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

PAGE 1-A



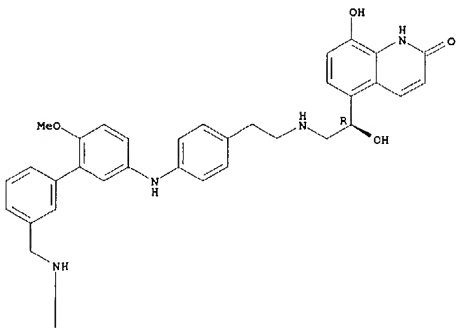
PAGE 2-A

RN 631915-10-1 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[[6-methoxy-3'-[[[(4-methoxyphenyl)methyl]amino]methyl][1,1'-biphenyl]-3-yl]amino]phenyl]ethyl]amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 1 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

PAGE 1-A



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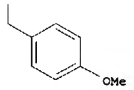

L4 ANSWER 2 OF 3 CA COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 138:401502 CA
TITLE: Preparation of aryl aniline .beta.-2 adrenergic receptor agonists
INVENTOR(S): Moran, Edmund J.; Jacobsen, John R.; Leadbetter, Michael R.; Nodwell, Matthew B.; Trapp, Sean G.; Aggen, James; Church, Timothy J.
PATENT ASSIGNEE(S): Theravance, Inc, USA
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003042164 | A1 | 20030522 | WO 2002-US36237 | 20021112 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004059116 | A1 | 20040325 | US 2003-642926 | 20030818 |

PRIORITY APPLN. INFO.: US 2001-338194P P 20011113
US 2001-343771P P 20011228
US 2002-292211 A1 20021112

OTHER SOURCE(S): MARPAT 138:401502
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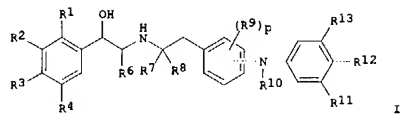
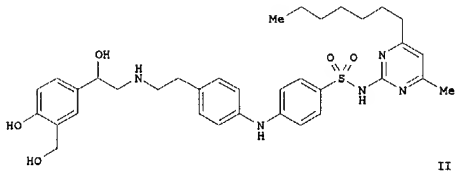
L4 ANSWER 2 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)



I



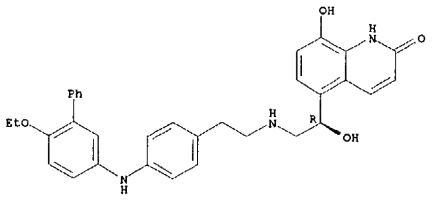
II

AB Title compds. I [R1-5 = H, alk(en/yn)yl, cycloalkyl, heterocyclyl, etc.; R6 = H, alkyl, alkoxy; R7 = H, alkyl; R8 = H, alkyl; R9 = alk(en/yn)yl, (hetero)aryl, etc.; R10 = H, alkyl; R11-13 = H, (cyclo)alkyl, alkenyl, alkynyl, (hetero)aryl, etc.; p = 0-4] are prepd. For instance, the di-Me ketal of 4-hydroxy-3-hydroxymethyl-.alpha.-bromoacetophenone (prepn. given) is reacted with 4-bromophenethylamine (CH2Cl2, Et3N) followed by 4,4'-dimethoxychlorodiphenylamine and subsequently reduced (THF, NaBH4). The resulting protected amino alc. is then coupled with N-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide (PhMe, dppf, Pd2dba3, 80.degree., 5 h) and then deprotected with HOAc (80.degree., 5 h) to give II. All of the compds. tested demonstrated greater binding at the .beta.2 adrenergic receptor than at the .beta.1 adrenergic receptor, i.e., Ki(.beta.1) > Ki(.beta.2); many with a selectivity greater than 20. I are useful for the treatment of pulmonary diseases.

IT **530084-66-3P 530084-87-8P 530117-33-0P 530117-43-2P 530118-10-6P 530118-11-7P 530118-12-8P 530118-13-9P 530118-17-3P 530118-19-5P 530118-20-8P 530118-21-9P 530118-24-2P 530118-25-3P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aryl aniline .beta.-2 adrenergic receptor agonists for treatment of pulmonary disorders)

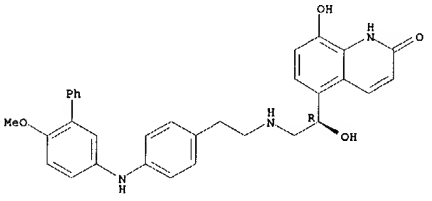
RN 530084-66-3 CA
CN 2(1H)-Quinolinone, 5-[(1R)-2-[[2-[4-[(6-ethoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]-1-hydroxyethyl]-8-hydroxy- (9CI) (CA INDEX NAME)

L4 ANSWER 2 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)
Absolute stereochemistry.



RN 530084-87-8 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[(6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]ethyl]- (9CI) (CA INDEX NAME)

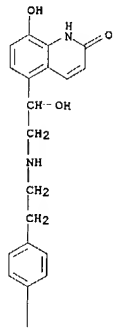
Absolute stereochemistry.



RN 530117-33-0 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[1-hydroxy-2-[[2-[4-[(6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]ethyl]-, hydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 2 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

PAGE 1-A



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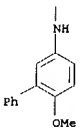
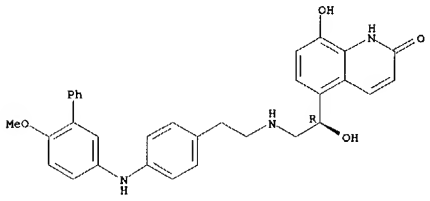


●x HCl

RN 530117-43-2 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[(6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]ethyl]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

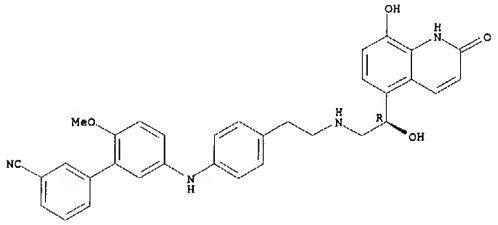
L4 ANSWER 2 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)



●x HCl

RN 530118-10-6 CA
CN [1,1'-Biphenyl]-3-carbonitrile, 5'-[[4-[2-[[(2R)-2-(1,2-dihydro-8-hydroxy-2-oxo-5-quinolinyl)-2-hydroxyethyl]amino]ethyl]phenyl]amino]-2'-methoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



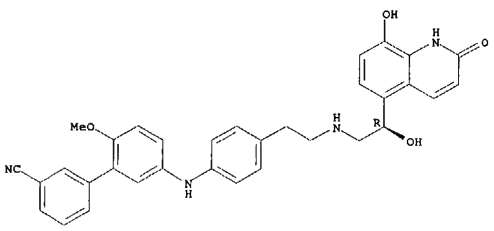
RN 530118-11-7 CA
CN [1,1'-Biphenyl]-3-carbonitrile, 5'-[[4-[2-[[(2R)-2-(1,2-dihydro-8-hydroxy-2-oxo-5-quinolinyl)-2-hydroxyethyl]amino]ethyl]phenyl]amino]-2'-methoxy-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 530118-10-6
CMF C33 H30 N4 O4

Absolute stereochemistry.

L4 ANSWER 2 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

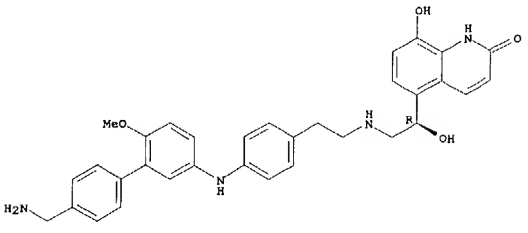


CM 2

CRN 76-05-1
CMF C2 H F3 O2

RN 530118-12-8 CA
CN 2(1H)-Quinolinone, 5-[(1R)-2-[[2-[4-[[4'-(aminomethyl)-6-methoxy[1,1'-biphenyl]-3-yl]amino]phenyl]ethyl]amino]-1-hydroxyethyl]-8-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



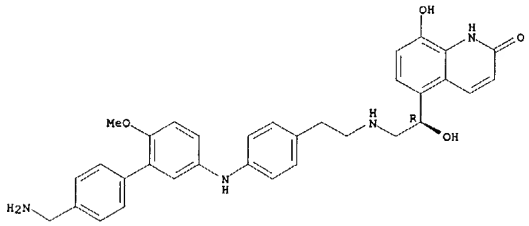
RN 530118-13-9 CA
CN 2(1H)-Quinolinone, 5-[(1R)-2-[[2-[4-[[4'-(aminomethyl)-6-methoxy[1,1'-

L4 ANSWER 2 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)
biphenyl]-3-yl]amino]phenyl]ethyl]amino]-1-hydroxyethyl]-8-hydroxy-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 530118-12-8
CMF C33 H34 N4 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

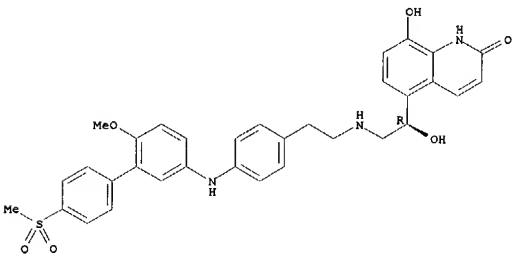
RN 530118-17-3 CA
CN [1,1'-Biphenyl]-4-carboxaldehyde, 5'-[[4-[2-[[(2R)-2-(1,2-dihydro-8-hydroxy-2-oxo-5-quinolinyl)-2-hydroxyethyl]amino]ethyl]phenyl]amino]-2'-methoxy-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 530118-16-2
CMF C33 H31 N3 O5

Absolute stereochemistry.

L4 ANSWER 2 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

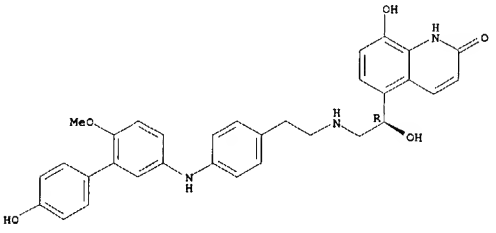


CM 2

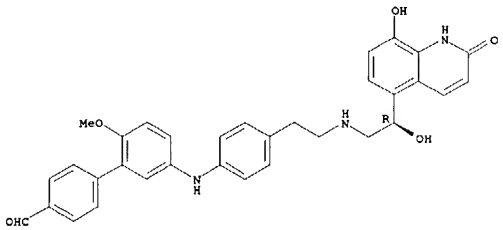
CRN 76-05-1
CMF C2 H F3 O2

RN 530118-20-8 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[(4'-hydroxy-6-methoxy[1,1'-biphenyl]-3-yl]amino]phenyl]ethyl]amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 2 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)



CM 2

CRN 76-05-1
CMF C2 H F3 O2

RN 530118-19-5 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[[6-methoxy-4'-(methylsulfonyl)[1,1'-biphenyl]-3-yl]amino]phenyl]ethyl]amino]ethyl]-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 530118-18-4
CMF C33 H33 N3 O6 S

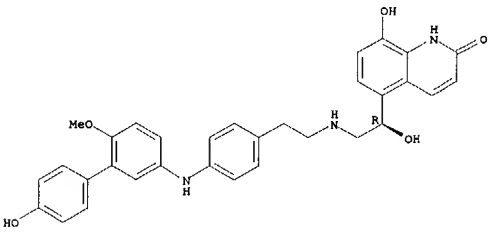
Absolute stereochemistry.

L4 ANSWER 2 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)
RN 530118-21-9 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[(4'-hydroxy-6-methoxy[1,1'-biphenyl]-3-yl]amino]phenyl]ethyl]amino]ethyl]-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 530118-20-8
CMF C32 H31 N3 O5

Absolute stereochemistry.



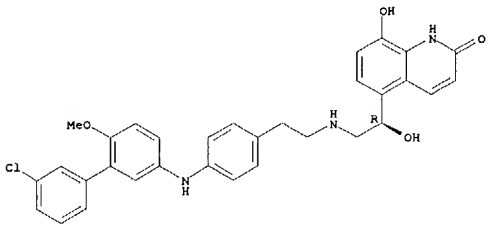
CM 2

CRN 76-05-1
CMF C2 H F3 O2

RN 530118-24-2 CA
CN 2(1H)-Quinolinone, 5-[(1R)-2-[[2-[4-[(3'-chloro-6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]-1-hydroxyethyl]-8-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 2 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

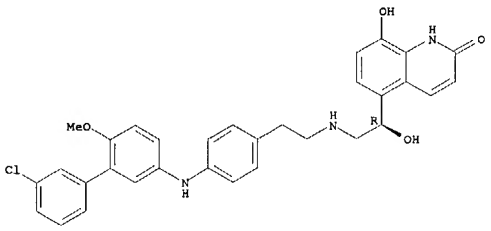


RN 530118-25-3 CA
CN 2(1H)-Quinolinone,
5-[(1R)-2-[[2-[4-[(3'-chloro-6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]-1-hydroxyethyl]-8-hydroxy-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 530118-24-2
CMF C32 H30 Cl N3 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

L4 ANSWER 2 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L4 ANSWER 3 OF 3 CA COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 138:401501 CA
TITLE: Preparation of aryl aniline .beta.-2 adrenergic receptor agonists
INVENTOR(S): Moran, Edmund J.; Jacobsen, John R.; Aggen, James
PATENT ASSIGNEE(S): Theravance, Inc., USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003042160 | A1 | 20030522 | WO 2002-US36188 | 20021112 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
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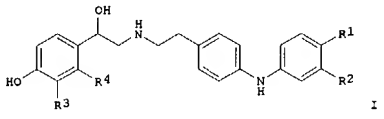
| US 2003153597 | A1 | 20030814 | US 2002-292211 | 20021112 |
| US 6653323 | B2 | 20031125 | | |
| US 2004059116 | A1 | 20040325 | US 2003-642926 | 20030818 |

PRIORITY APPLN. INFO.: US 2001-338194P P 20011113
US 2002-292211 A1 20021112

OTHER SOURCE(S): MARPAT 138:401501
GI

L4 ANSWER 3 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)



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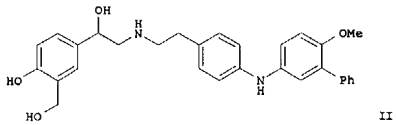


II

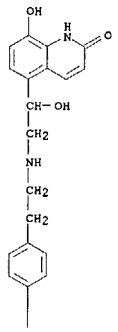
AB Title compds. I [R1 = methoxy, ethoxy; R2 = H, Ph or R1 = H and R2 = phenyl; R3 = CH2OH, NHCHO; R4 = H or R3-4 = taken together are NHC(O)CH=CH] are prepd. For instance, the di-Me ketal of 4-hydroxy-3-hydroxymethyl-.alpha.-bromoacetophenone (prepn. given) is reacted with 4-bromophenethylamine (CH2Cl2, Et3N) followed by 4,4'-dimethoxychlorodiphenylamine and subsequently reduced (THF, NaBH4). The resulting protected amino alc. is then coupled with 4-methoxy-3-phenylaniline (PhMe, dppf, Pd2dba3, NaOBu-t, 80.degree., 5 h) and then deprotected with HOAc (80.degree., 5 h) to give II. All of the compds. tested demonstrated greater binding at the .beta.2 adrenergic receptor than at the .beta.1 adrenergic receptor, i.e., Ki(.beta.1) > Ki(.beta.2); many with a selectivity greater than 20. I are useful for the treatment of pulmonary diseases.

IT **530084-34-5P 530084-35-6P 530084-43-6P 530084-53-8P 530084-66-3P 530084-87-8P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aryl aniline .beta.-2 adrenergic receptor agonists for treatment of pulmonary disorders)

RN 530084-34-5 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[1-hydroxy-2-[[2-[4-[(6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]ethyl]-, monohydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 3 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

PAGE 1-A



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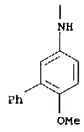
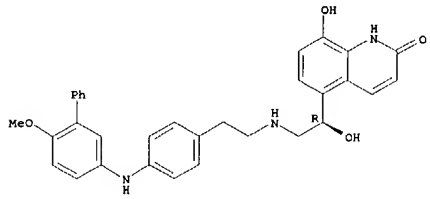


● HCl

RN 530084-35-6 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[(6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]ethyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

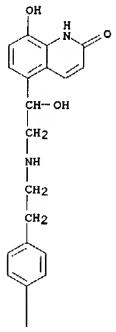
L4 ANSWER 3 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)



● HCl

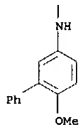
RN 530084-43-6 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[1-hydroxy-2-[[2-[4-[(6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]ethyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



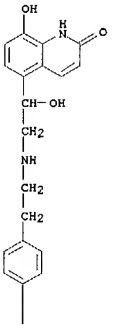
L4 ANSWER 3 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

PAGE 2-A



RN 530084-53-8 CA
CN 2(1H)-Quinolinone, 5-[2-[[2-[4-[(6-ethoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]-1-hydroxyethyl]-8-hydroxy- (9CI) (CA INDEX NAME)

PAGE 1-A



L4 ANSWER 3 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)

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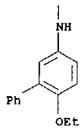
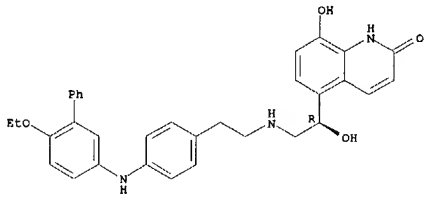


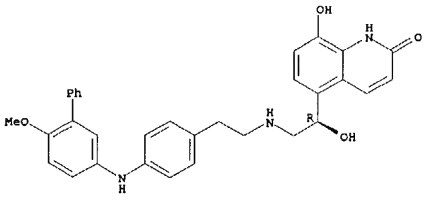
RN 530084-66-3 CA
CN 2(1H)-Quinolinone, 5-[(1R)-2-[[2-[4-[(6-ethoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]-1-hydroxyethyl]-8-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 530084-87-8 CA
CN 2(1H)-Quinolinone, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[2-[4-[(6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]ethyl]amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS

L4 ANSWER 3 OF 3 CA COPYRIGHT 2004 ACS on STN (Continued)
RECORD. ALL CITATIONS AVAILABLE IN THE RE
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L6 ANSWER 1 OF 3 MARPAT COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 140:16568 MARPAT
TITLE: Preparation of aryl aniline .beta.-2 adrenergic receptor agonists
INVENTOR(S): Moran, Edmund J.; Jacobsen, John R.; Leadbetter, Michael R.; Nodwell, Matthew B.; Trapp, Sean G.; Aggen, James; Church, Timothy J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 68 pp., Cont.-in-part of U.S. Ser. No. 292,835.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003229058 | A1 | 20031211 | US 2003-431762 | 20030508 |
| US 6670376 | B1 | 20031230 | US 2002-292835 | 20021112 |
| US 2004059116 | A1 | 20040325 | US 2003-642926 | 20030818 |
| US 2004063755 | A1 | 20040401 | US 2003-643196 | 20030818 |
| PRIORITY APPLN. INFO.: | | | US 2001-338194P | 20011113 |
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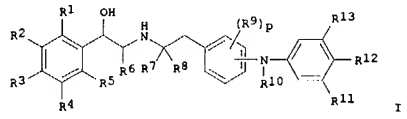

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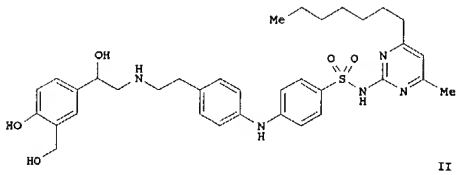
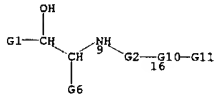


II

L6 ANSWER 1 OF 3 MARPAT COPYRIGHT 2004 ACS on STN (Continued)

AB Title compds. I [R1-5 = H, alk(en/yn)yl, cycloalkyl, heterocyclyl, etc.; R6 = H, alkyl, alkoxy; R7 = H, alkyl; R8 = H, alkyl; R9 = alk(en/yn)yl, (hetero)aryl, etc.; R10 = H, alkyl; R11-13 = H, (cyclo)alkyl, alkenyl, alkynyl, (hetero)aryl, etc.; p = 0-4] are prepd. For instance, the di-Me ketal of 4-hydroxy-3-hydroxymethyl-.alpha.-bromoacetophenone (prepn. given) is reacted with 4-bromophenethylamine (CH2Cl2, Et3N) followed by 4,4'-dimethoxychlorodiphenylamine and subsequently reduced (THF, NaBH4). The resulting protected amino alc. is then coupled with N-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide (PhMe, dppf, Pd2dba3, 80.degree., 5 h) and then deprotected with HOAc (80.degree., 5 h) to give II. All of the compds. tested demonstrated greater binding at the .beta.2 adrenergic receptor than at the .beta.1 adrenergic receptor, i.e., Ki(.beta.1) > Ki(.beta.2); many with a selectivity greater than 20. I are useful for the treatment of pulmonary diseases.

MSTR 1



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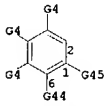
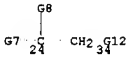
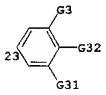


G2 = 24-9 34-16

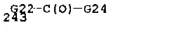


G4 = OH
G10 = NH
G11 = 23

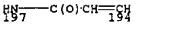
L6 ANSWER 1 OF 3 MARPAT COPYRIGHT 2004 ACS on STN (Continued)



G12 = phenylene (SO (1-) G13)
G22 = O
G31 = Ph (SO (1-) G46)
G32 = 243



G44+G45= 197-6 194-1



MPL: claim 1
NTE: or pharmaceutically acceptable salts and solvates
NTE: additional substitution also claimed
STE: or stereoisomers

L6 ANSWER 2 OF 3 MARPAT COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 138:401502 MARPAT
TITLE: Preparation of aryl aniline .beta.-2 adrenergic receptor agonists
INVENTOR(S): Moran, Edmund J.; Jacobsen, John R.; Leadbetter, Michael R.; Nodwell, Matthew B.; Trapp, Sean G.; Aggen, James; Church, Timothy J.
PATENT ASSIGNEE(S): Theravance, Inc, USA
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003042164 | A1 | 20030522 | WO 2002-US36237 | 20021112 |
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| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004059116 | A1 | 20040325 | US 2003-642926 | 20030818 |
| PRIORITY APPLN. INFO.: | | | US 2001-338194P | 20011113 |
| | | | US 2001-343771P | 20011228 |
| | | | US 2002-292211 | 20021112 |

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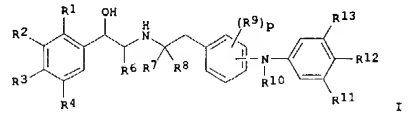
L6 ANSWER 2 OF 3 MARPAT COPYRIGHT 2004 ACS on STN (Continued)



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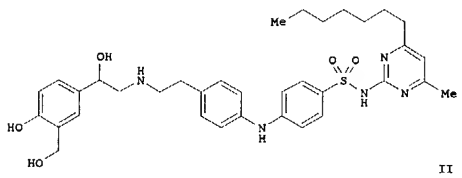
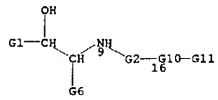


II

AB Title compds. I [R1-5 = H, alk(en/yn)yl, cycloalkyl, heterocyclyl, etc.; R6 = H, alkyl, alkoxy; R7 = H, alkyl; R8 = H, alkyl; R9 = alk(en/yn)yl, (hetero)aryl, etc.; R10 = H, alkyl; R11-13 = H, (cyclo)alkyl, alkenyl, alkynyl, (hetero)aryl, etc.; p = 0-4] are prepd. For instance, the di-Me ketal of 4-hydroxy-3-hydroxymethyl-.alpha.-bromoacetophenone (prepn. given) is reacted with 4-bromophenethylamine (CH2Cl2, Et3N) followed by 4,4'-dimethoxychlorodiphenylamine and subsequently reduced (THF, NaBH4). The resulting protected amino alc. is then coupled with N-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide (PhMe, dppf, Pd2dba3, 80.degree., 5 h) and then deprotected with HOAc (80.degree., 5 h) to give II. All of the compds. tested demonstrated greater binding at the .beta.2 adrenergic receptor than at the .beta.1 adrenergic receptor, i.e., Ki(.beta.1) > Ki(.beta.2); many with a selectivity greater than 20. I are useful for the treatment of pulmonary diseases.

MSTR 1

L6 ANSWER 2 OF 3 MARPAT COPYRIGHT 2004 ACS on STN (Continued)



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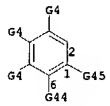

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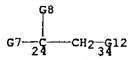
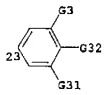
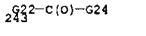


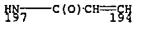
G4 = OH
G10 = NH
G11 = 23



G12 = phenylene (SO (1-) G13)
G22 = O
G31 = Ph (SO (1-) G46)
G32 = 243



G44+G45= 197-6 194-1



L6 ANSWER 2 OF 3 MARPAT COPYRIGHT 2004 ACS on STN (Continued)

MPL: claim 1
NTE: or pharmaceutically acceptable salts and solvates
NTE: additional substitution also claimed
STE: or stereoisomers

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 3 MARPAT COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 138:401501 MARPAT
TITLE: Preparation of aryl aniline .beta.-2 adrenergic receptor agonists
INVENTOR(S): Moran, Edmund J.; Jacobsen, John R.; Aggen, James
PATENT ASSIGNEE(S): Theravance, Inc., USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003042160 | A1 | 20030522 | WO 2002-US36188 | 20021112 |
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| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2003153597 | A1 | 20030814 | US 2002-292211 | 20021112 |
| US 6653323 | B2 | 20031125 | | |
| US 2004059116 | A1 | 20040325 | US 2003-642926 | 20030818 |
| PRIORITY APPLN. INFO.: | | | US 2001-338194P | 20011113 |
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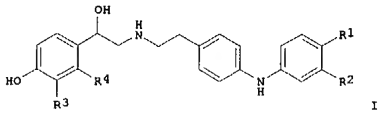
L6 ANSWER 3 OF 3 MARPAT COPYRIGHT 2004 ACS on STN (Continued)



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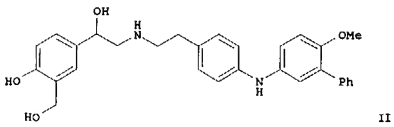

II

AB Title compds. I [R1 = methoxy, ethoxy; R2 = H, Ph or R1 = H and R2 = phenyl; R3 = CH2OH, NHCHO; R4 = H or R3-4 = taken together are NHC(O)CH=CH] are prepd. For instance, the di-Me ketal of 4-hydroxy-3-hydroxymethyl-.alpha.-bromoacetophenone (prepn. given) is reacted with 4-bromophenethylamine ($CH_2Cl_2$, $Et_3N$) followed by 4,4'-dimethoxychlorodiphenylamine and subsequently reduced (THF, $NaBH_4$). The resulting protected amino alc. is then coupled with 4-methoxy-3-phenylaniline (PhMe, dppf, Pd2dba3, NaOBu-t, 80.degree., 5 h) and then deprotected with HOAc (80.degree., 5 h) to give II. All of the compds. tested demonstrated greater binding at the .beta.2 adrenergic receptor than at the .beta.1 adrenergic receptor, i.e., Ki(.beta.1) > Ki(.beta.2); many with a selectivity greater than 20. I are useful for the treatment of pulmonary diseases.

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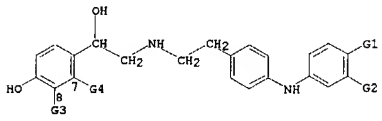
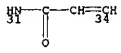


L6 ANSWER 3 OF 3 MARPAT COPYRIGHT 2004 ACS on STN (Continued)

G1 = OMe
G2 = Ph
G3 +G4 = 31-8 34-7



MPL: claim 1
NTE: or pharmaceutically acceptable salts or solvates
STE: or stereoisomers

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L4              3 S L3

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L5              4 S L1 FULL
L6              3 S L5/COM

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